Case Reports

Severe Hypoglycemia Associated With Disopyramide

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DISOPYRAMIDE PHOSPHATE (NORPACE) has been widely used in the United States in recent years. It is a structurally unique antiarrhythmic agent with pharmacologic properties similar to quinidine.[1] Most adverse effects of disopyramide are attributable to its anticholinergic action, but recently uncommon but serious cardiac toxicities that include heart failure and an atypical ventricular tachycardia have been reported.[2,3] Goldberg and co-workers[4] recently described a case in which hypoglycemia developed in a patient following disopyramide treatment. We report two additional cases in which the use of disopyramide is associated with severe hypoglycemia and lactic acidosis.

Reports of Cases

CASE 1. A 74-year-old man was admitted to the University of Wisconsin Hospital (Madison) in October 1977 following a syncopal episode. He was first admitted to hospital in September 1974 in severe congestive heart failure when digoxin and diuretic therapy was instituted. He was readmitted in October 1976 for evaluation of recurrent syncopal episodes. A Holter monitor recording showed periods of sinus bradycardia, frequent runs of ventricular tachycardia and a brief period of slow idioventricular rhythm of 34 beats per minute. A demand pacemaker was implanted in October 1976 and quinidine sulfate therapy was started. The patient did well until September 1977, when he was admitted with congestive heart failure. He improved on treatment and was discharged on a regimen of procainamide hydrochloride, spironolactone, digoxin, furosemide and hydralazine hydrochloride.

At the time of admission in October 1977, he stated he had no chest pain, palpitations, dyspnea, orthopnea or paroxysmal nocturnal dyspnea. On physical examination he had a blood pressure of 100/60 mm of mercury and pulse rate of 72 beats per minute; scattered bilateral rales were heard over the lung bases. A chest x-ray study showed cardiomegaly, a right pleural effusion and the pacemaker electrode in the right ventricular apex. An electrocardiogram showed that he had a normally functioning pacemaker. Admission laboratory tests gave normal values.

A 24-hour Holter monitor recorded the presence of frequent premature ventricular contractions and short runs of ventricular tachycardia. The patient had received 500 mg of procainamide orally at midnight, 6 AM and noon on the day of admission. Procainamide (1 gram) was given at 6 PM. Shortly after midnight on day 2, he received 450 mg of disopyramide orally. At 1:30 AM the patient was noted to be hypotensive (systolic blood pressure was 54 mm of mercury); he then had a seizure. An intravenous infusion of metaraminol bitartrate solution was started and the blood pressure became stable. Within an hour the patient was conscious and responsive. The metaraminol infusion was discontinued and his hemodynamic state continued to be stable. At 8:30 AM the patient again became acutely hypotensive and an infusion of metaraminol solution was restarted, again stabilizing the blood pressure. He was alert and oriented. At 10:15 AM he had a generalized seizure and cardiopulmonary arrest. He was successfully resuscitated and use of a respirator was begun. Tests of blood specimens drawn at 8:36 AM showed a blood glucose level of 9 mg per dl. Immediately after the arrest, the blood glucose level was 47 mg per dl and 50 grams of dextrose solution was given intravenously. The electrocardiogram showed widened QRS and prolonged QT-U with giant U waves and a rate of 80 beats per minute before returning to a paced rhythm.

Pertinent and abnormal laboratory values are given in Table 1. Noteworthy are persistently low blood glucose and high lactate levels.

The blood pressure remained low despite therapy with direct-acting pressor agents; initially, dopamine hydrochloride and later norepinephrine (levarterenol) bitartrate were administered in combination with sodium nitroprusside. At least three 50-ml boluses of 50 percent dextrose solution were given during the next 24 hours. On day 3 at 9:15 PM he was found pulseless and was pronounced dead.

CASE 2. A 58-year-old man was admitted to William

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TABLE 1.—*Laboratory Values in Case 1*

Day and Time	Serum Glucose mg/dl (N=70-100)	Serum Potassium mEq/liter (N=3.8-5.0)	Blood Po_2 mm/Hg (N=95-100)	Serum pH (N=7.35-7.45)	Serum Lactate mEq/liter (N=0.2-1.2)	Comments
Day 1	108	5.2	...	...	...	Procainamide, 500 mg given by mouth × 3 doses, and 1 gram at 6 PM*
Day 2						
8:36 AM	9	4.4	...	...	...	Disopyramide, 450 mg given by mouth shortly after midnight; 1:30 AM patient hypotensive and had a seizure; 8:30 AM patient hypotensive
10:15 AM	47	4.8	55	7.12	9.6	Generalized seizure and cardiopulmonary arrest; 50 percent dextrose in water solution given
12:00 PM	322	...	109	7.38	11.4	Blood pressure remained low despite dopamine and norepinephrine given in combination with nitroprusside. A bolus of 50 percent dextrose in water given throughout the next 24 hours
5:20 PM	79	...	126	7.52	3.1	
10:00 PM	149	5.2	...	...	...	
Day 3						
3:00 AM	51	5.2	...	...	12.3	
7:30 AM	51	5.8	...	...	...	
8:00 AM	43	...	...	...	...	
9:00 AM	...	...	...	...	12.9	
11:46 AM	86	5.5	94	7.42	17.2	
3:00 PM	56	...	...	...	10.6	
9:15 PM	...	...	...	...	...	Pronounced dead

*The patient's serum creatinine level on admission was 2.7 mg/dl and had risen to 5.3 mg/dl on the morning of day 3.

S. Middleton Memorial Veterans Administration Hospital (Madison) in May 1979 with a history of recurrent ventricular tachycardia. Four years before admission, a Bjork-Shiley aortic valve was implanted for calcific aortic stenosis, which was complicated by an intraoperative myocardial infarction. Postoperatively, he had mitral regurgitation and congestive heart failure. Ventricular arrhythmias developed and multiple antiarrhythmic drugs had been given in an attempt to control his ventricular arrhythmia, with limited success.

On admission he gave a history of a recent increase in symptoms of ventricular tachycardia, including palpitations, lightheadedness and weakness. Medicines being taken at the time of admission were quinidine, propranolol hydrochloride, warfarin, furosemide, potassium chloride, nitroglycerin, digoxin and diazepam.

On physical examination he was noted to be thin and pale and had a blood pressure of 110/80 mm of mercury, a pulse rate of 84 beats per minute and 18 respirations per minute. The prosthetic valve sounds were normal.

Admitting laboratory studies showed a low hematocrit level, a prolonged prothrombin time and serum electrolyte values within normal limits. An electrocardiogram showed a first-degree AV block and a nonspecific intraventricular conduction defect. The quinidine therapy was discontinued and disopyramide, 200 mg, was given by mouth every six hours starting on the first hospital day. The propranolol dosage was increased to 20 mg given every six hours. Serum disopyramide concentration 48 hours after the first dose showed a peak of 2.6 μg per ml and a trough of 1.8 μg per ml. On the third hospital day, an episode of ventricular tachycardia occurred and was terminated with the intravenous administration of lidocaine hydrochloride. On the tenth hospital day, he had abdominal pain and his extremities were cold. He vomited and was found to be pale, diaphoretic and having labored respirations. He was hypotensive with a palpable systolic blood pressure of 70 mm of mercury. An electrocardiogram showed a widened QRS and prolonged PR and QT intervals. He then had a cardiopulmonary arrest and resuscitation was initiated. Calcium gluconate and sodium bicarbonate were administered and the electrocardiogram abnormalities corrected.

The pertinent laboratory findings are listed in Table 2. The very low serum glucose and high serum potassium and lactate levels are striking. A glucose solution was given intravenously and administration of the disopyramide and propranolol was discontinued. The patient recovered but was lost to follow-up.

Discussion

Two cases of severe hypoglycemia occurred in patients who had received disopyramide. In both instances, the patients' serum glucose level was less than 10 mg per dl and was associated with hypotension and lactic acidosis. The first patient had a severe reaction within 90 minutes after administration of a single dose of disopyramide, though hypoglycemia was not reported until eight hours later. The sequence of events and available laboratory findings obtained after a second hypotensive episode and seizure strongly suggest they were related to hypoglycemia.

In the second case, the temporal relationship of hypoglycemia and disopyramide is not as clear. The

TABLE 2.—*Laboratory Values in Case 2*

Day and Time	Serum Glucose mg/dl (N=70-100)	Serum Potassium mEq/liter (N=3.8-5.0)	Serum pH (N=7.35-7.45)	Serum Lactate mEq/liter (N=0.2-1.2)	Plasma Bicarbonate mEq/liter (N=21-28)	Comments
Day 1	112	3.6	...	...	22	Disopyramide, 200 mg given by mouth every 6 h; propranolol, 20 mg, given by mouth every 6 h; continue warfarin, furosemide, potassium chloride, digoxin and diazepam administration
Day 10						
8:00 AM	113	5.4	...	...	18	
10:00 AM	...	6.5	7.20	...	<8	Pale, diaphoretic, hypotensive; transferred to coronary care unit
11:00 AM	...	...	...	12.3	...	
12:00 PM (immediately after arrest)	4	8.5	...	12.1	...	Cardiopulmonary arrest; calcium gluconate and sodium bicarbonate given
2:00 PM	5	6.6	...	...	...	Dextrose, 50 percent in water, given

patient had a normal serum glucose level earlier that day. He had been taking disopyramide for ten days without prior evidence of hypoglycemia.

In a recent review of drug-induced hypoglycemia, Seltzer[5] notes several predisposing factors. These include restricted carbohydrate intake, increasing age, alcohol intake and abnormal liver or renal function. The second patient was receiving propranolol concurrently with the disopyramide and had recently had his propranolol dose increased. Propranolol has been reported to cause hypoglycemia.[6-9] This may have contributed to the severity of his hypoglycemia but because he had been receiving propranolol for over a year before this incident, it is not likely to have been the sole cause.

The relationship between hypoglycemia and lactic acidosis is not clear in these patients. Lactic acidosis can be due to inadequate tissue perfusion with increased production of lactate or a reduction in hepatic lactate extraction (or both).[10] Both patients were hypotensive before blood specimens were drawn.

Disopyramide has been reported to cause significant myocardial depression.[2,11] Perhaps disopyramide decreased cardiac output in these patients by decreasing contractility or by causing an atypical ventricular tachycardia that resulted in inadequate tissue perfusion. Hypoglycemia may occur as a consequence of reduced hepatic blood flow, though this is uncommon.[12]

The first patient was noted to have a generalized seizure, which can also be a cause of lactic acidosis.[10] If there were a defect in hepatic lactate uptake this could result in both lactic acidosis and hypoglycemia due to a decrease in a gluconeogenic substrate.[10]

Medalle and associates[13] reported three cases of lactic acidosis and hypoglycemia; in one of these the lactic acidosis resolved with the administration of glucose alone. They felt that hypoglycemia in the presence of hepatic damage could impair the hepatic uptake of glucose precursors including lactate, which would then lead to decreased gluconeogenesis and increased hypoglycemia.

Whether the hypoglycemia or the lactic acidosis occurred first remains speculative. In neither case was disopyramide toxicity or idiosyncrasy suggested at the time hypoglycemia was found. There have been more than 30 cases of hypoglycemia associated with disopyramide therapy reported to the manufacturer, most of the patients being asymptomatic with glucose levels ranging from 50 to 60 mg per dl (E. N. Shubert, PhD, Searle Laboratories, oral communication, July 15, 1980). In addition, pilot studies in animals and humans have shown a trend for glucose lowering by disopyramide. The mechanism of action is unknown.

Goldberg and colleagues[4] reinduced hypoglycemia in their patient with administration of disopyramide. The precise mechanism was not determined but disopyramide did not cause an increase in insulin release or a suppression of glucagon, whereas the glucose levels fell. The incidence of symptomatic hypoglycemic reactions to disopyramide appears to be low but clinically important and, in unusual circumstances, perhaps life threatening. Further controlled studies are needed to fully assess the mechanism of action and predisposing factors for such an effect.

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